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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,228	05/17/2005	Sharon D Boggs	PU5028USW	5668

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EXAMINER	
NOLAN, JASON MICHAEL	
ART UNIT	PAPER NUMBER
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,228	BOGGS ET AL.	
	Examiner	Art Unit	
	Jason M. Nolan, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-16,18,19 and 41* is/are rejected.

7)☒ Claim(s) *12,17 and 20-24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/17/05 & 5/9/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-24 & 41 are currently pending in the instant application; of which: **Claims 3-13, 15, 16 & 18-24** are currently amended and **Claim 41** is new. **Claims 25-40** are cancelled.

Priority

This application is a 371 of PCT/US03/35808, filed on 11/12/2003. Acknowledgement is made of Applicants' claim for benefit of US Provisional Patent Application 60/428,374, filed on 11/22/2002. Said claim has been made in the oath and first paragraph of the Specification.

Information Disclosure Statement

Applicants' information disclosure statements (IDS), filed on 05/17/2005 and 05/09/2006 have been considered. Please refer to Applicants' copies of the 1449 submitted herein.

Sequence Listing

Acknowledgement is made of Applicants' submission of a sequence listing. Said sequence listing has been entered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

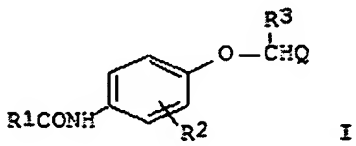
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

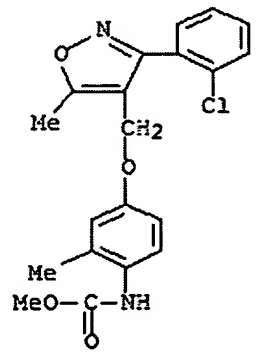
The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Sato *et al.* (JP 11263775 A, 09/28/**1999**). Taught in the Japanese patent are compounds according to formula I and the species, shown below, wherein **Z** = -C(O)N(R^8)- and **R^5** = R^6O-.

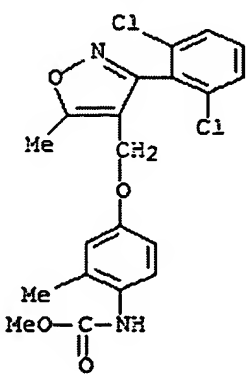


I

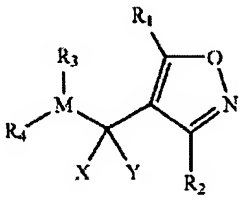
RN 244175-45-9

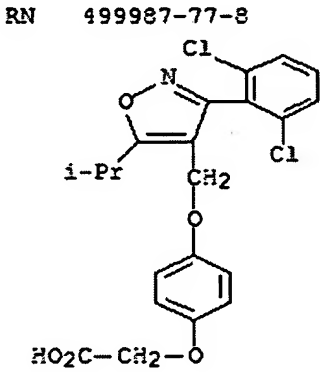


RN 244175-46-0



Claims 1-7, 9, 11 & 13-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Bauer *et al.* (US Patent 7,034,046 with priority to 07/01/**2002**; see IDS WO 3003/015771). Taught in the patent is compound RN 499987-77-8 according to the formula in claim 1 wherein **Z** = OR^4 and $\mathbf{R^5}$ = CO_2R^6, shown below.





Claim Rejections - 35 USC § 112, 1st

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 & 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of formula (I), and salts and solvates thereof, the specification does not reasonably provide enablement for "physiological functional derivatives thereof". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)*. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:

(A) *The breadth of the claims;*
(B) *The nature of the invention;*
(C) *The state of the prior art;*
(D) *The level of one of ordinary skill;*
(E) *The level of predictability in the art;*
(F) *The amount of direction provided by the inventor;*
(G) *The existence of working examples; and*
(H) *The quantity of experimentation needed to make or use the invention based on the content of the disclosure.*

The breadth of the claims - The nature of the invention

Claim 1 is drawn to 1,2-oxazoles according to formula (I), wherein the definitions of **Z, Y, $R^{1, 2, 3 \& 5}$, a, b & c** are defined therein. Compounds according to formula (I) are useful as pharmaceuticals. Furthermore, pharmaceutically acceptable salts, solvates, and physiological functional derivatives thereof are encompassed by this claim (and **Claim 41**).

The state of the prior art & the level of predictability in the art

With respect to pharmaceutically acceptable salts, solvates, and physiological functional derivatives thereof, the state of the art is more advanced for solvates and salts, than it is for "physiological functional derivatives." Said term includes esters, amides, and prodrugs (specification, page 23). Esters and amides are indicative of the chemical design, however these examples do not limit the term. Prodrugs are included in this broad term. The state of the prior art is that prodrugs are an inactive form of a drug that exerts its effects after metabolic processes within the body converts it to a usable or active form. In other words, a prodrug is a drug that must be activated before it can produce a physiological effect. Prodrugs are designed to be appended to a particular functional group such as a carboxylic acid, alcohol, amine, phosphate, or phosphonic acid. Research is required to match the prodrug with the particular drug to overcome challenges including stability, rate of systemic prodrug cleavage, and safety. Furthermore, it needs to be decided what enzyme system is wanted to cleave the prodrug followed by the evaluation of the prodrug analogs in assays to measure progress in achieving the desired properties (stability, solubility, cleavage of prodrug in biological matrices, pharmacokinetics in animal models, efficacy in animal models, and safety in animal models). This process is exactly like the process used to discover the active drug. The difficulty of discovering effective prodrugs is often underestimated and for all of the aforementioned reasons, the claimed invention is highly unpredictable.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance, which would allow the skilled artisan to extrapolate from the disclosure and examples provided, to use the claimed method commensurate in the scope with the instant claims. The only guidance with respect to salts, solvates and derivatives of formula (I) are the definitions located on page 23 of the specification.

The existence of working examples

There has not been provided sufficient evidence that would warrant the skilled artisan to accept the data and information provided in the working examples as correlative proof that *any* derivative as claimed, would be able to be synthesized using the methods outlined in the specification. Furthermore, no examples have been presented for any salts, solvates and derivatives of a compound according to formula (I).

The level of the skill in the art and the quantity of experimentation needed

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that discovering effective prodrugs is often underestimated and the process mimics the process conducted to discover the active drug. Thus, the specification fails to provide sufficient support for the broad use of a prodrug of a compound according to formula (I).

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 states, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which prodrug design (functional group manipulation) will work for this class of compounds to determine if they would be encompassed in the instant claims, with no assurance of success. *This rejection can be overcome by deleting the unsupported language.*

Claims 15, 16, 18 & 19 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for compounds/compositions and a method for *the treatment of some conditions mediated by FXR in a subject*; does not reasonably provide enablement for 1) *the prophylaxis of any conditions mediated by FXR in a subject, or* 2) *the treatment of some conditions medicated by FXR; such as*: fibrosis of any organ. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The nature of the invention

The nature of the invention is compounds and compositions of Formula I, the process for preparing these compounds, and methods of using these compounds as pharmaceuticals.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art, namely pharmacological art, involves screening *in vitro* and *in vivo* to determine if the compounds exhibit desired pharmacological activities, which are then tested for their efficacy on human beings. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the claimed invention is highly unpredictable since one skilled in the art would recognize that a group of compounds and compositions may provide a treatment for cardiovascular diseases, liver diseases, liver fibrosis, increasing HDL cholesterol, and lowering triglycerides, but it does not mean that the same group of compounds and

compositions may *prevent* cardiovascular diseases, liver diseases, liver fibrosis, increasing HDL cholesterol, and lowering triglycerides.

More specifically, the currently claimed invention is drawn to compounds that are useful as agonists of the farnesoid X receptor (FXR). FXR is a recently discovered member of the nuclear hormone superfamily. "Members of the nuclear hormone receptor superfamily function as ligand-activated transcription factors to regulate genetic networks controlling cell growth and differentiation, inflammatory responses, and metabolism. The ability to modulate nuclear receptor-dependent gene expression with small molecules has made the superfamily a favored target for drug discovery... small molecules that regulate receptors for activity are currently used to treat a number of human disorders..." (Schulman *et al.* (*Chemistry & Biology* **2004**, *11*, 639-646). FXR has activity similar to that seen in other steroid receptors such as estrogen or progesterone but more similar in form to early-year *orphan receptors* PPAR, LXR and RXR. From Schulman *et al.*, "...over the last ten years a combination of molecular, genetic, and biochemical approaches along with the nuclear receptor platform assays have been used to identify ligands for orphan receptors and uncover new signaling pathways."

Recent reviews on FXR have established FXR as targets in cardiovascular diseases (Bishop-Bailey *et al. PNAS* **2004**, *101(10)*, 3668-3673); and as having a critical role in the control of cholesterol, lipid, and glucose metabolism (Caron *et al. Endocrinology* **2006**, *147(9)*, 4022-4024; Claudel *et al. Arteriosclerosis, Thrombosis, and Vascular Biology* **2005**, *25*, 2020-2030).

The amount of direction or guidance present and the presence or absence of working examples

There is no direction or guidance provided which supports Applicant's claimed method for the *prophylaxis* of cardiovascular diseases, liver diseases, and liver fibrosis as indicated. The direction or guidance present in Applicants' Specification for a method of using the compounds and compositions of Formula I to *treat* clinical conditions such as cardiovascular diseases, liver diseases, liver fibrosis, as well as increasing HDL cholesterol and lowering triglycerides is found on pages 1-2, 24-28 & 103-110. Found therein are *in vitro* binding assays establishing the compounds of the instant application as agonists of the farnesoid X receptor (pp. 103-110).

The breadth of the claims, quantity of experimentation, and level of skill in the art

Claims 15, 16, 18 & 19 are drawn to "a method for the treatment or prophylaxis ..." Prophylaxis is commonly known to be synonymous with prevention. In order to prevent a disease, one would need to precisely identify those subjects likely to acquire such a disease, administer Applicant's claimed invention, and then demonstrate that if the identified subject did not develop the disease, such an effect was the direct result of administration of the claimed invention.

Because of the aforementioned reasons, a person of skill in the art could not practice the claimed invention herein, or a person of skill in the art could practice the claimed invention herein only with undue experimentation and with no assurance of success.

In order to overcome this rejection, Examiner suggests deleting **Claim 15**, deleting the word "prophylaxis" in **Claims 16, 18 & 19,** and amendment the scope of **Claim 19** from organ fibrosis to liver fibrosis.

Claim Objections

Claims 12, 17 & 20-24 are objected to as being dependent upon a rejected base **Claim 1**, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 13 is objected to because of the following informalities: a composition is a mixture of two or more elements, and as claimed: the composition consists only of a compound of claim 1. Examiner suggests importing the additional elements listed in Claim 14 into Claim 13 and canceling Claim 14. Appropriate correction is required.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason M. Nolan, Ph.D.** whose telephone number is **(571) 272-4356** and electronic mail is **Jason.Nolan@uspto.gov**. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph M^{c}Kane** can be reached on **(571) 272-0699**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1626

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER

Joseph K. M^{c}Kane
Supervisory Patent Examiner
Art Unit 1626
Date: February 27, 2007